Young women's stroke etiology differs from that in young men: an analysis of 511 patients

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Abstract

Women are known to have particular heterogeneity in stroke etiology related to childbearing and hormonal factors. Although there are continued acute stroke treatment advances focusing on clot dissolution or extraction, effective secondary prevention of stroke, however, is dependent on an accurate etiological determination of the stroke. Otherwise, more strokes are likely to follow. Analysis of young women's stroke etiology in a large stroke registry incorporating contemporary neurovascular and parenchymal imaging and cardiac imaging. Young people (18-49 years old) with stroke were consecutively accrued over a 4 year period and an investigative protocol prospectively applied that incorporated multimodality magnetic resonance imaging, angiography, cardiac echo and stroke relevant blood investigations. All patients were classified according to an expanded Trial of Org 10172 in Acute Stroke Treatment – TOAST – classification and neurological deficit by the National Institute of Health stroke admission scores. In 511 registry derived, young stroke patients (mean age 39.8 years, 95% confidence interval: 39.1; 40.7 years), gender (women n=269, 53%) the etiological categories (women; men) included: i) small vessel disease (30/55;25/55), ii) cardioembolic (16/42;26/42), iii) large vessel cervical and intracranial disease (24/43;19/43), the *other category* (132/226; 91/226), which included, iv) substance abuse (15/41; 26/41, 4.6), v) prothrombotic states (22/37;15/37), vi) dissection (11/30;19/30), vii) cerebral venous thrombosis (15/19; 4/19, 12.4), viii) vasculitis (8/12; 4/12), ix) migraine related (10/11, 1/11) and x) miscellaneous vasculopathy (38/52;14/52). The latter entities comprised of aortic arch atheroma, vessel redundancy syndrome, vertebrobasilar hypoplasia, arterial fenestrations and dolichoectasia. Some conditions occurred solely in women, such as eclampsia (5), Call Fleming syndrome (4), fibromuscular dysplasia (3) and Moya Moya syndrome (2). Categories aside from bland infarction included: ii) intracerebral hemorrhage (43/106; 63/106) and xiii) stroke of undetermined etiology (6/10; 4/10). Admission mean National Institute of Health Stroke Scale scores differed significantly between women and men (4.7; 6.0 t=1.8, P=0.03). Young women's stroke is significantly different from men in 7/12 stroke etiological categories in addition to 4 unique subtypes that require specific management.

Introduction

The etiological identification in young stroke patients, ages <49 years, has been challenging. In this population, the traditional risk factors for stroke such as high blood pressure, hyperlipidemia, or coronary vascular disease are much less frequent.[1] Young patients with stroke are often misdiagnosed on initial presentation to the emergency room, especially if they have posterior circulation stroke.[2] Notable advances in the past two decades included multimodality magnetic resonance imaging techniques with improved evaluation and there are now several population-based studies of stroke etiology in young adults. The average annual incidence of stroke in patients' ages 15-49 based on studies in Sweden, Italy, United Kingdom, and in Finland is estimated to be 8.7-11.3 per 100,000.[1,3-7] Currently there are no studies specifically comparing stroke etiologies between young men and women. Younger women are known to have unique stroke predisposing factors related to pregnancy and hormonal factors.

The aim of the present study was to identify and compare stroke etiologies unique to men and women.

Materials and Methods

Clinical and investigative data

This was a prospective study conducted from September 2002 to December 2006 with consecutive collection of clinical, radiological, sonographic and laboratory data. Only patients with first ever stroke were included in the study. Consecutive patients with stroke, aged 18-49 years were accrued through a prospectively coded dedicated stroke registry in a tertiary referral center. The registry was approved by the University Institutional Review Board and in compliance with HIPAA (Health Insurance Portability and Accountability Act) regulations. All patients signed informed consent for the evaluation and the collection of the their neurological, medical and neurocognitive data. Analysis of the stroke mechanism subtypes was performed retrospectively.

Ischemic stroke was defined as acute onset of focal neurological deficits with correlating imaging evidence of stroke. Neurological deficits were classified by National Institute of Health (NIH) stroke scale. All patients were evaluated by a stroke neurologist and an investigative protocol was applied using magnetic resonance (MR) imaging brain, MR angiography, echocardiography and stroke relevant blood investigations. A modified version of the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification was used that defines 5 subtypes of ischemic stroke, large-artery atherosclerosis, cardioembolism, small-vessel occlusion, stroke of other determined etiology, and stroke of undetermined etiology.[8] For our study the majority of the young patients fell under the subtype of *other*, therefore etiology of stroke was classified by expanded TOAST classification to include: large vessel cerebrovascular disease, small vessel cerebrovascular disease, cardiogenic, dissection, prothrombotic states, migraine induced (type 3a and 3b Welch), cerebral venous thrombosis, vasculitides, vasculopathy other miscellaneous and unknown.[9]

Statistical analysis

Descriptive analysis, including means, 95% confidence intervals and standard deviations for continuous variables and frequency distributions for categorical variables, were obtained for all study parameters. T-tests were

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used to compare means and a P value of ≤0.05 was regarded as significant. Associations between continuous variables were analyzed using Pearson's product moment correlation. All analyses were run in SAS version 9.1. The etiological classifications included in the models were cardioembolic, hemorrhage, large vessel disease, small vessel disease, other and unknown. These independent variables were also coded as binary (yes/no). Stepwise multivariate logistic regression analyses were used to determine the significant etiological and topographical associations.

Results

Demographics

Of the 511 young patients (mean age 39.8 y, 95% CI: 39.1;40.7 y) with women (n=269, 53%, mean age 39.8 y, 95% CI: 39.1;40.7 y) and men (40.0 y, 95% CI: 38.7, 41.3 y) with gender distribution of young women stroke patients representing n=269 or 53% and first time stroke patients numbered 363.

Stroke scores and etiology

Admission mean NIHSS scores differed significantly between women (4.7) and men (6.0) (t=1.8, P=0.03). Both men and women had similar stroke subtypes of small vessel disease (women 30/55; men 25/55, 0.09, P=NS), and large vessel cervical and intracranial disease (women 24/43; men 19/43, 0.19, P=NS). Men however had a greater number of the subtype due to cardioembolism (26/42 3.9 P=0.05) compared to women. In the remaining 29 (5.7%) patients, multiple etiological possibilities were found and these were accordingly labeled indeterminate etiologies. Women on the other hand, had greater numbers of the subtype *other* (132/226, 6.8 P=0.01) (Figure 1). These subtypes added together translated into a total of 396 instances in 363 patients as in 33 (9.1%) patients more than one etiology (range 2-5) was determined it was not possible to state with certainty which was causative.

Overall a significant number of the young stroke patients (226/363) fell under the subtype of *other*, thus the expanded TOAST classification was applied. Both men and women did not have significant differences in etiologies of prothrombotic states (22/37;15/37, 0.74 P=NS) and dissection (11/30;19/30, 3.2, P=NS). Men did show a greater etiology of substance abuse (26/41, 4.6, P=0.05). Women showed a greater ischemic stroke etiology of cerebral venous thrombosis (15/19, 12.4, P=0.001), vasculitis (8/12; 23.1, P=0.001), migraine related (10/11, 6.6, P=0.02) and miscellaneous vasculopathy (38/52; 9.7, P=0.01) (Figure 2). In the remaining 24 patients, classification could not be achieved confidently, as multiple stroke mechanisms were possible particularly substance abuse and prothrombotic states in addition to the other categories. These have been labeled indeterminate etiologies.

Under the category of miscellaneous vasculopathy, both young men and women shared etiologies in the subtypes of; aortic arch atheroma, vessel redundancy syndrome, vertebrobasilar hypoplasia, arterial fenestrations and dolichoectasia.

Some conditions occurred solely in women, such as eclampsia (n=5), Call Fleming syndrome (n=4), fibromuscular dysplasia (n=3) and Moya Moya syndrome (n=2).

Categories aside from ischemic infarction, included (women;men) intracerebral hemorrhage (43/106; 63/106, P=0.01) and stroke of undetermined etiology (6/10; 4/10, 0.2, P=NS).

Discussion

Our study focuses on comparing and contrasting stroke etiologies of women and men. Just under half (n=226/511; 44%) had non-traditional etiologies for stroke. This concurs with a recently published study of 87 young stroke patients <45 years old, revealing that

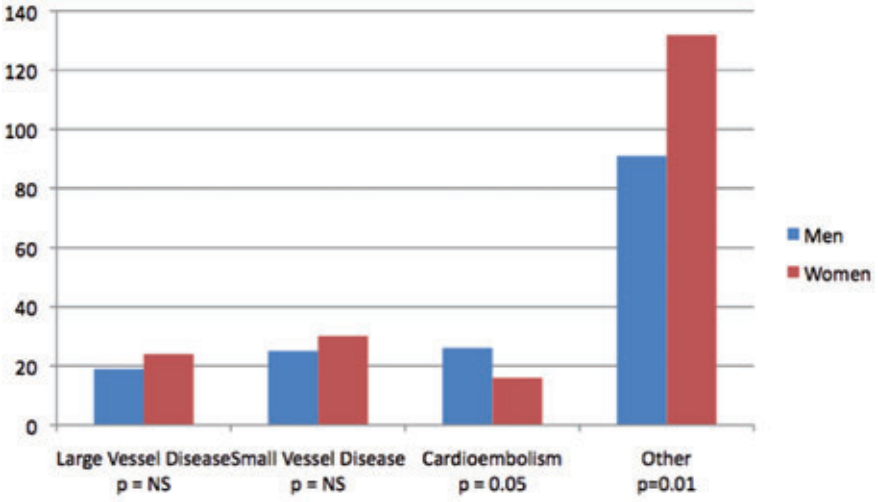

Figure 1. Stroke etiology (TOAST categories) in men and women (X axis: stroke subtype and Y axis: number of strokes).

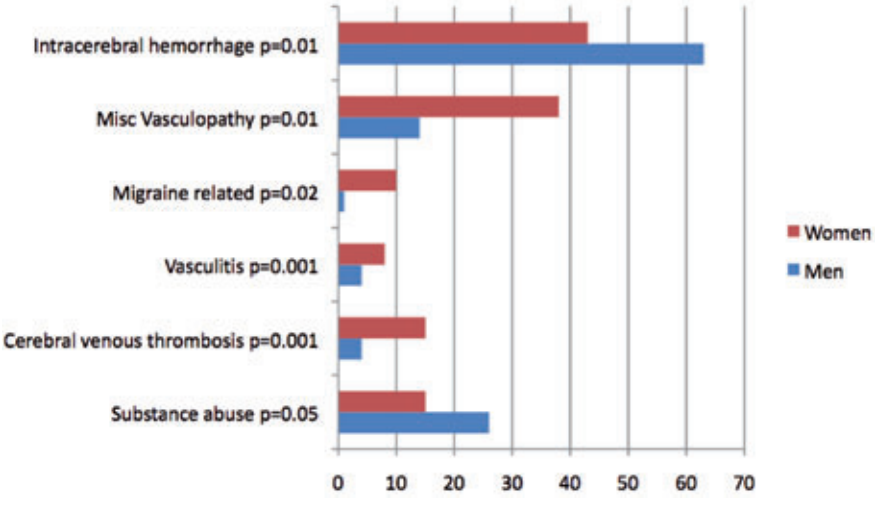

Figure 2. Stroke Etiology in the expanded *other* category (Y axis: etiology, X axis: number of strokes).

the most frequent stroke etiology found was also the *other* entity,[10] as well other studies with 34%,[3] and one with 1008 patients with 26% of other etiology.[1] In our study where 44 % had stroke due to other etiology and more women than men had a stroke etiology within the *other* category. The *other* category also included a group of miscellaneous entities and a generic vasculopathy was the most common stroke etiology for women. The four unique conditions that were only found in women stroke patients under this category were: eclampsia, fibromuscular dysplasia, Call Fleming syndrome and moyamoya syndrome. Using the expanded TOAST classification to include more rare etiologies for stroke helps guide stroke management, prevention of future strokes and tailor the treatment approach for young patients with stroke.

Women (ages 15-44) with preeclampsia have an increased risk of ischemic stroke, postpartum and peripartum due to disrupted cerebral autoregulation.[11] As preeclampsia is related to endothelial dysfunction, women with a history of preeclampsia overall have a 60% more likelihood in the future to have a non-pregnancy related ischemic stroke compared to women without a history of preeclampsia.[11-14] Cerebrovascular fibromuscular dysplasia is a rare disease in which the intracranial arteries, more commonly the internal carotid, are at increased risk of stenosis from artery tissue abnormality rather than atherosclerotic or inflammatory mechanisms.[15,16] It has been estimated that women comprise 2/3 of patients with fibromuscular dysplasia with intracranial artery involvement, and the reason why remains unknown.[15] Call Fleming or reversible cerebral arterial vasoconstriction (RCAV) is a rare condition that presents clinically with severe, recurrent, *thunderclap* headaches, occasional transient or fluctuating neurological abnormalities and radiologically with transient reversible vasoconstriction of the circle of Willis.[17] Through an investigation of case reports, women and young patients (ages 20-50) appear to be the most commonly affected.[18] Moyamoya was found to have a female: male ratio ranging from 2.8:1.6 in the United States in an international systemic review.[19]

Also in the *other* category, women compared to men, showed a greater number of stroke etiology numbers consequent to cerebral venous thrombosis, vasculitis, and migraine related (Welch Classification 3a and 3b).[20] Cerebral venous thrombosis is more common in pregnancy related stroke, often occurring in the postpartum period.[13] The relationship between migraine in young women and stroke remains controversial. Young women with migraine history who also have coexistence of oral contraceptive use, hypertension, or smoking have an even greater risk for ischemic stroke.[11,14,21] Evaluation of genes encoding endothelial function as possible candidates for migraine and strokes susceptibility showed that variants in endothelin-1 and endothelin receptor type B may increase stroke risk in white women ages 15-49.[22] The risk of stroke in young women with migraine with aura is estimated to be 17-19 per 100,000; while the risk of stroke of non-aura migraine remains unknown.[14] One study estimated that of the young women with a history of migraine who had strokes, between 20-40% had strokes that developed directly from their migraine attack.[20]

Our study did however differ in some respects from other young stroke studies. Many studies evaluating stroke in young patients, also often list cardioembolism as a frequent etiology hence, this may be consistent finding.[1,10,23] In fact cardioembolism may be the most frequent or one of the most common causes however in our study this accounted for 11.6% but even the most recent large studies showed a wide variation (19.6-47%).[1,3] There was also variation in the entity of multiple etiologies which were very common (26%) in the largest study of young stroke (Putaala *et al*.) whereas in our study this was 5.7%. Methodological variability is purported to be the most likely factor in this regard with geographic, race ethnicity other possibilities. Cardioembolism was also more frequent in men than women in one study (Ji *et al.*) although significance was in the marginal category.[3] The present study also found that men had more strokes with etiologies related to cardioembolism and substance abuse.

Men and women showed no etiological difference in prothromboic states and dissection as well as SVD and LVD. In northern Sweden 21% of their young adult ischemic strokes had unknown etiology according to the modified TOAST criteria with spontaneous cervical arterial dissection as the leading probable etiology.[6] Overall women had lower mean NIH stroke scores (women 4.7; men 6; and more rare/non-traditional etiologies for stroke related to pregnancy and vascular abnormality (fibromuscular dysplasia, Moya Moya syndrome). This may indicate that, overall women are at more risk for possible misdiagnosis and thus strokes. Men had significant ischemic stroke etiology of cardioembolism and substance abuse, both eminently treatable causes. Intracerebral hemorrhage occurred more frequently in men and the leading causes in both men and women were arteriovenous malformations, aneurysms substance abuse followed by hypertensive related. With regards to multiple etiological categories (5.7%) in this series, a similar result (2%) was noted by a very recent study (Ji *et al*).[3]

A limitation of this study is the registry-based nature, rather than population based analysis. In addition, identification of risk factors responsible or etiology remains imprecise because of the frequent occurrence of more than one risk factor or stroke mechanism that sometimes act in concert.

Conclusions

Although acute stroke treatment advances focus on clot dissolution or extraction, prevention is more effective in terms of the population at large. Effective secondary prevention of stroke, is however, dependent on an accurate etiological determination of the stroke, otherwise, more strokes are likely to follow. In this study, young women's stroke was significantly different from men in 7/12 stroke etiological categories (cardioembolism, cerebral venous thrombosis, vasculitis, migraine, vasculopathy, substance abuse, intracerebral hemorrhage) in addition to 4 unique subtypes that require specific management. Hence, due attention to the expanded diagnostic classification and gender specificity may assist in identification of the diverse etiology of stroke in young people.

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